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KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
PETERSEN, CLARK D	

ART UNIT	PAPER NUMBER
1655	

DATE MAILED: 06/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/606,162	REMACLE ET AL.	
	Examiner	Art Unit	
	Clark D. Petersen	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *16-21 and 30-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 22-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *6/25/2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, claims 1-29, as well as the species elections of PAK6/MKK3/CDK8 in claim 15 and chemical treatment in claim 27, in the reply filed on May 2, 2006, is acknowledged.

Claims 16-21 and 30-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on May 2, 2006. Claims 1-15 and 22-29 were examined on their merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear how a coefficient provided by analysis of a purified phosphoprotein would be used to correct data collected by the method of claim 5; specifically it is not clear which data would be corrected.

Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Enablement is considered in view of the Wands factors (MPEP 2164.01 (A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: Claim 15 is drawn to a method of evaluating cell activation by evaluating the phosphorylation state of specific, named proteins from the list of Table I in the specification. Further, the claim is restricted according to the restriction requirement sent March 27, 2006 and the responsive election filed May 2, 2006, to the determination of cell activation by measuring phosphorylation of CDK8, PAK6, and MKK3.

Breadth of the claims: The claims are narrow in that applicant proposes to measure an aspect of cell activation by studying three cellular proteins in particular, namely CDK8, PAK6, and MKK3.

Guidance of the specification and existence of working examples: The specification provides guidance generally in determining the level of phosphorylation of a protein, or a cascade of proteins, in a comparison of activated versus untreated cells. Specific examples are given in the working examples of experiments performed with Akt, Erk, p38, as a few examples. However no working examples are given for determining phosphorylation status of CDK8, MKK3, or PAK6, and mention of these kinases is absent elsewhere in the specification, other than in Table 1 which provides guidance for the claims.

Predictability and state of the art: Studying phosphorylation of cellular proteins is a well-accepted method of studying aspects of cell physiology. It is reasonable to characterize the phosphorylation of members of signaling cascades along with changes in cellular dynamics. However CDK8 is unique among CDKs in that it appears that its activation is not dependent on phosphorylation as is observed with other CDK family members. Hoeppner et al (2005) determined that CDK8 is lacking the threonine in its activation loop that is present in other CDKs, and is phosphorylated to activate such CDKs. Rather CDK8 is activated by interaction of the residue that replaces the otherwise-phosphorylated threonine with its binding partner Cyclin C (see Possible mechanisms of CDK8 Activation, pp. 839-840, for example).

Therefore, no evidence is provided in either the instant specification for determination of activation of CDK8 by phosphorylation, and there is evidence in the literature that phosphorylation of CDK8 is not an effective means of determining cellular activation state.

Amount of experimentation necessary: As discussed above, the instant specification describes generally a method of characterizing cellular physiological responses to activating stimuli by measuring phosphorylation of components of cellular signaling cascades. It provides working examples for measuring phosphorylation of members of a few pathways including Akt, ERK, and p38, among others. However the instant specification does not provide working examples of phospho-specific antibodies for the elected species CDK8 and PAK6 and it is therefore not detailed enough to allow one of ordinary skill in the art to perform a cell activation assay using phosphorylation of these signaling molecules as a readout.

In view of the lack of guidance from the specification, the absence of working examples, literature that undermines the assertions of the instant application, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore claims 1 and 15, as they are drawn to the elected species of the combination of CDK8, PAK6, and MKK3, are not considered to be enabled by the instant specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 11-12, 14, 22, and 23-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Paweletz, et al (2001). Paweletz et al teach a method of microdissecting distinct cell populations, from within and from around a tumor, from a single patient. They collect cellular lysates and immobilize them on slides made of nitrocellulose and glass. They analyze the phosphorylation state of Akt, and ERK, for example, and correlate it with tumor progression, which reads on evaluating an activated state of cells (see Results, p. 1985, Fig. 5, p. 1986, and Materials and Methods pp. 1987-1988, for example). Therefore the teachings of Paweletz et al are deemed to anticipate the claims cited above in the instant application.

Claims 1, 2 and 13, 22, 26, and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al (2001).

Lee et al teach that it is possible to activate cells with a chemical treatment, in this case a transfection mixture comprising a transfectable plasmid for beta-pix, which leads to phosphorylation of MKK3 and the transcription factor ATF-2. They demonstrate that they can determine the ratio of phosphorylated MKK3 and ATF-2 to unphosphorylated MKK3 and ATF-2 with an antibodies specific to phospho-MKK3 and

phospho-ATF2, and use it measure activation of these proteins in cells activated with the beta-Pix transfection mixture vs. untreated cells (see Materials and Methods, pp.25067-25068, and see Fig. 5, p. 25069, as examples). Therefore the teachings of Lee et al are deemed to anticipate the claims cited in the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9, 11-12, 14-15, 22-27, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paweletz et al (2001) in view of Huang (2001). The teachings of Paweletz et al were discussed above and are applied as before. Paweletz et al do not teach the use of an antibody as a capture molecule.

Huang teaches a method of preparing a microarray utilizing antibodies as capture molecules, for comparing treated versus untreated samples. Huang teaches that by preparing a support with antibodies to specific cytokines, and exposing them to conditioned media from different cancerous cell lines, he can demonstrate that different types of cancerous cells secrete different types of cytokine (see Materials and Methods, pp.2-4, Results p. 6, and Fig. 4. pp. 6-7, as examples).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use protein-specific antibodies immobilized onto a support as

capture molecules in the method of determining phosphorylation state of candidate proteins from differentially treated cell lysates taught by Paweletz et al, because Huang teaches that it is possible to study differences in individual proteins by spotting their antibodies onto a support and capturing specific proteins for study, rather than entire proteomes. Huang even suggests that his method would be useful for studying posttranslational modifications, a category that includes protein phosphorylation (see p. 12, paragraph 2, for example). One would have been motivated to combine the methods because Huang teaches that antibody capture microarray method is simple, and allows accurate measurement of the difference in individual protein levels between two samples, which is difficult to achieve with other methods.

Based upon the teachings of the cited references, the level of skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paweletz et al in view of Huang et al, and further in view of Gustafson et al (US Patent # 5413939, issued 5/9/1995). The teachings of Paweletz et al and Huang et al are discussed above and applied as before. Paweletz et al and Huang et al do not teach that metals, compact discs and electronic devices can be used in a method of testing cell activation.

Gustafson et al describe a method of binding antigens or antibodies to a compact disc, adding the complementary antigen or antibody, and then testing interferometrically

the binding of antigen to antibody. Gustafson et al also teach that metals can be used for immobilizing protein with the expectation of measuring binding properties of complementary molecules (see col. 1, lines 29-36).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a metal surface, or a compact disc, and do measurements electronically in a method of determining cell activation by measuring binding of phosphospecific antibodies to immobilized phosphoproteins, because Gustafson et al teach that one can bind proteins to a metal surface or compact disc, and then efficiently test binding of antibodies to the immobilized proteins, in the instant situation using the technique of interferometry. One would have been motivated to do so, because Gustafson et al teach that their system is characterized by high linearity, a large dynamic range, a background free output, few process steps, short incubation times, and low coefficient of variation in relation to a standard measurement (see col. 2, lines 10-29, for example). Gustafson et al also teach that immobilizing proteins on metal surfaces allows light to reflect, making possible detection of changes in wavelength of that reflected light which can be correlated with binding of an analyte, such as an antibody.

Based upon the teachings of the cited references, the level of skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paweletz et al in view of Huang et al, and further in view of Chang et al (USPGPub US2002/0192654 A1, filed 6/15/2001). The teachings of Paweletz et al and Huang et al are discussed above and applied as before. Paweletz et al and Huang et al do not expressly teach the use of glass, silicon or plastic as solid supports for phosphoproteins in a method of determining cell activation.

Chang et al teach that it is well known in the art to use silicon, glass or plastic as a bio-chip substrate for DNA or protein immobilization (see Page 1, paragraph 0002, for example). They teach that the concept of the biochip was developed in the late twentieth century, and that the biochip is broadly defined as a product for immobilizing DNA, protein, or cell structures on glass, silicon or plastic plate for biochemical analysis.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a plastic, glass, or silicon support in a method of measuring phosphoproteins in for the purpose of determining cell activation, because determining cell activation depends on immobilizing phosphoproteins on a solid support, and Chang et al teach that glass, plastic and silicon are useful as supports for immobilized proteins. One would have been motivated to do so because Chang et al teach that use of silicon, glass, or plastic biochips for study of proteins is useful because it is associated with high reliability, and rapid and accurate analysis (see para [0002], for example).

Based upon the teachings of the cited references, the level of skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention.

Claims 22 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paweletz et al in view of Matsui et al (EMBO J, 1996). The teachings of Paweletz et al were discussed above and are applied as before. Paweletz et al do not teach the treatment of cells after lysis with a compound, and testing the response of kinase activity within the lysate to a test compound.

Matsui et al teach a method of lysing cells and concentrating a particular kinase activity from the cell lysate. They then provide various cellular proteins as substrates for the kinase activity. They demonstrate that adding a test compound to the kinase changes its activity toward cellular protein substrates; in this case, addition of GTPγS changes the phosphorylation activity of the kinase complex towards its substrates S6 protein, Protein Kinase C, and Myelin Basic Protein (MBP) (see Materials and Methods, p2214-2215, and Fig. 4, p. 2210, as examples).

It would have been obvious to one of skill in the art at the time the invention was made to use the method of Matsui et al of isolating lysate-kinase activity first, and then applying a test compound, in the method of testing phosphorylation equilibrium by binding phosphoproteins to a solid support, because Matsui et al demonstrate that it is possible to measure a change in phosphorylation status of a substrate by stimulating a kinase activity after cells have already been lysed. One would have been motivated to do so because Matsui et al demonstrate that one can concentrate kinase activity and thus have a stronger readout, a benefit cited above as a benefit of the method of Huang.

Based upon the teachings of the cited references, the level of skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Clark D. Petersen whose telephone number is (571)272-5358. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on (571)272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

CDP

6/5/2006

Terry McKelvey

TERRY MCKELVEY, PH.D.
SUPERVISORY PATENT EXAMINER